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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/868,779	08/20/2001	Keisuke Teshigawara	3813-0101P	6309

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EXAMINER
PURI, BEENA

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 01/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/868 779	TESHIGAWARA ET AL
Examiner	**Art Unit**
Beena Puri	1633

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1 136(a) In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U S C § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment See 37 CFR 1 704(b)

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL** 2b)☒ This action is non-final

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C D 11, 453 O G 213

Disposition of Claims

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-8 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1 85(a).

11)☐ The proposed drawing correction filed on _____ is a)☐ approved b)☐ disapproved by the Examiner

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S C § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17 2(a)).

* See the attached detailed Office action for a list of the certified copies not received

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U S C § 119(e) (to a provisional application)

a)☐ The translation of the foreign language provisional application has been received

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U S C §§ 120 and/or 121

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4)☐ Interview Summary (PTO-413) Paper No(s) _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim(s) 5-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 5-8 are drawn to the composition of lymphocytes subsets-NK cells prepared by a said method for the use in immune therapy.

The instant invention is to an effective immune therapy treatment for cancer patients in terminal stage. It is noted that the specification teaches about the procedure used for separating lymphocytes subsets-NK cells from the blood. The specification teaches that B7 gene, which is incorporated into an expression vector, is expressed into K562 cells class 1 antigen deficient cancer cells derived from human chronic myelocytic leukemia. The specification further teaches that human lymphocytes and K562 cells expressing B7 gene are combined and incubated in a medium containing IL-2, human serum, and mitomycin to stop the amplification of the K562 cells. However, the instant claims are not enabled because the specification fails to show the experimental data regarding the expression of B7 gene in K562 cells before combining with lymphocytes.

The instant claims are directed to the composition of lymphocytes for the use in immune therapy. Thus, the nature of the invention falls in the realm of immunotherapy. The state of the art of immunotherapy using lymphocytes subsets-NK cells is in it's infancy and plagued by unpredictability. The following references have been cited herein to illustrate the state of the art of immunotherapy related to lymphocytes subsets-NK cells. **Hernberg** (1999) recites in a review article: "To enable further development of immunotherapy we need to know more about the mechanisms involved in host defense, especially when the system is influenced by extrinsic factors, that is immunomodulative agents" (See abstract, pg. 145). He further indicates: "whether lymphocytes subsets have any value as prognostic markers in patients with malignancies receiving therapy is still unclear" (See conclusion section on pg. 150). **Porgador** et al (1997) recites: "NK cells have been long considered as an option for cancer therapy particularly for patients bearing class I-suppressed cancers. However, no studies of autologous NK lines as a potential tool for treatment of such patients have been reported" (See Introduction column 2, pg. 13140). They further recite: " Loss of class I expression is a common phenotype within some cancers and specific T cell therapy might augment emergence of such cells. However, reinforcement with adoptively transferred autologous NK cells could prevent this outcome and moreover, NK therapy could yield positive bystander effects for specific T cell therapy, i.e., activated NK cells are a major source of secreted interferon-γ which enhances antigen processing and presentation by class I and II MHC molecule" (See Discussion, pg. 13145). **Atzpodien** et al (1993) states: "The physiologic and therapeutic role of NK cells in cancer, remains to be defined in more details. It is

still unresolved whether NK cells by themselves mediate tumor regression in vivo, or whether NK function presents a mere reflection of the underlying immune status, which plays an as yet undisclosed role in the development and therapeutic regression of human malignancies" (See Discussion section, pg. 358)

The above references acknowledge the usefulness of lymphocytes subsets-NK cells as prognostic markers for cancer patients receiving immunomodulative therapy in the future, however, they also illustrate that there are numerous obstacles that the specification would need to overcome. As such, the disclosed claims are very broad and are not enabled because the specification fails to teach a protocol to deliver effective amount of lymphocytes in the cancer patient. Applicants have not provided guidance in the specification toward specific immune therapy treatment protocol, which would avoid the many obstacles in utilizing mainly lymphocytes subsets-NK cells to treat and prevent cancer in a patient. Further, the specification does not provide any working examples of treating and preventing cancer by immunotherapy. Without guidance from the specification or the prior art, empirical experimentation would be required to determine an effective amount to prevent and treat a specific cancer in different types of mammal.

To attempt to practice the claimed invention, one of skill in the art would turn to the specification for guidance in practicing the invention. As set forth above, however, the specification lacks sufficient guidance to surmount the technical difficulties recognized in the art. Another source of guidance for one skilled in the art, the prior art, again for reasons set forth above, also lacks solutions to overcome the considerable list of obstacles recognized in the field. In the absence of working examples from the speci-

fication and the prior art. one of skilled in the art would resort to experimentation to navigate the obstacles to practicing the claimed invention. Again. as established above. solutions to these technical problems have been elusive despite an enormous amount of experimentation due to a number of factors, including the unpredictable nature of the art. Such unpredictability would warrant even more experimentation, with no true expectation of a measure of success. The amount of experimentation required to practice the claimed invention embodiments would necessitate undue experimentation on the part of one skilled in the art.

In conclusion, given the nature of the invention, the state of the art, the lack of predictability found in the art, the breadth of the claims, the amount of guidance set forth in the specification, and the working example set forth it is concluded that the amount of experimentation necessary to practice the invention is very high and is in fact undue.

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 1-8 are rejected under 35 U. S. C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is directed to "A method for in vitro culture of lymphocytes comprising incubating lymphocytes and cells in which a particular gene has been expressed in a particular cancer cell or in which such a particular cancer has already been expressed, to amplify mainly NK cells or none-MHC-bound or MHC-bound killer T cells and further to amplify killer T cells specific to a cancer antigen" renders the claim indefinite because

it is unclear whether the limitation(s) following the phrase are part of the claimed invention. Claim as written is not clearly pointed out because it is reciting in vitro culture assay for lymphocytes, expressing cancer gene, and amplifying NK cells, MHC-bound killer T cells etc. See MPEP § 2173.05(d). Claims 2-8 are rejected under 35 U.S.C. 112, second paragraph, as being dependent on claim 1.

3. ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim(s) 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 690 125 A2 (Tadao, O) and further in view of Martin-Fontecha et al., (1998).

Claims1-4 are drawn to a method for in vitro culture of lymphocytes involves incubating lymphocytes and cells in which a particular gene has been expressed in a particular cancer lines or cells, which are deficient in expression of a class 1 antigen and the particular gene has already been expressed, to amplify mainly NK cells or none-MHC-bound or MHC-bound killer T cells and further to amplify killer T cells specific to a cancer antigen. Claim is further drawn in vitro culture of lymphocytes with cells expressing B7 gene with cancer antigen gene or gene for a cell-binding factor.

Tadao teaches a process for an induction of lymphocyte having cell killing activities against a tumor cell which comprises the step of coculturing a tumor tissue

containing tumor cell and lymphocyte of autologous peripheral blood obtained from a subject (See abstract, page 1). Tadao teaches the activation of lymphocytes by immunomodulators (See page 4, example 1).

Martin-Fontecha teaches B7 molecules can interact with receptors on NK cells (See abstract, page 5910). Martin-Fontecha further teaches B7-2 expressing tumor cell lines (See column 2, page 5910).

The artisan would have been motivated to develop a method to amplify NK cells by combining the teachings of Tadao and Martin-Fontecha. The ordinary artisan would have been motivated to amplify lymphocyte subsets-NK cells in vitro culture that involves incubation of lymphocytes and cancer cells or cells which are expressing a particular gene and are deficient in expression of a class 1 antigen. Furthermore, the person of ordinary skill in the art would have been motivated to combine the human lymphocyte and K562 cancer cells expressing B7 gene and incubated in a media containing IL-2. By coculturing together, lymphocytes will be activated by immunomodulators (IL-2) and further lymphocyte subsets-NK cells will be stimulated by B7 molecules expressed by cancer cells K562 transfected with B7 gene. The artisan would have a reasonable expectation of success for the proliferation of T lymphocyte subsets-NK cells stimulated by B7 gene because of the teachings of Tadao and Martin-Fontecha. Therefore, the invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Beena Puri, Ph. D. whose telephone number is (703)-

306-0284. The examiner can normally be reached on 8:00 a. m. EST. to 4:30 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703)-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are (703)-308-4242 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)-308-0196.

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/1630

Beena Puri, Ph. D.
Patent Examiner
AU1633

bp
Nov. 30, 2001.